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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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09/485,062 05/05/00 HOLZEMANN

G MERCK2075

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EXAMINER

LUNTON, D	
ART UNIT	PAPER NUMBER

1653
DATE MAILED:

11/09/01

15

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.

09/486,062

Applicant(s)

Holzemann

Examiner

David Lukton

Art Unit

1653



-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on Aug 17, 2001

2a) ☒ This action is FINAL.

2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 35 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) 1, 2, 4-8, and 11-31 is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) 1, 2, 4-8, and 11-31 is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirements.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.

2. ☐ Certified copies of the priority documents have been received in Application No. _____.

3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☐ Notice of References Cited (PTO-892)

18) ☐ Interview Summary (PTO-413) Paper No(s) _____

16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

19) ☐ Notice of Informal Patent Application (PTO 152)

17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____

20) ☐ Other

Pursuant to the directives of paper No. 13 (filed 8/1/01), claims 1, 2, 4-8, 20 have been amended, claims 3, 9, 10 cancelled, and claims 21-23 added. At that point, claims 1, 2, 4-8, 11-23 were pending. Subsequently, paper No. 14 (filed 8/17/01) directed the addition of claims 24-31. Accordingly, claims 1, 2, 4-8, 11-31 are pending.

Applicants arguments filed 8/1/01 have been considered and found persuasive in part.

✱

The following is a quotation of the first paragraph of 35 U.S.C. §112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 5-8 and 21 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

In response to a previously imposed enablement rejection, applicants have provided a declaration which asserts that a few of the claimed compounds are effective to antagonize $\alpha_v\beta_3$ *in vitro*. This evidence is sufficient to support claims that are drawn to compounds *per se*, pharmaceutically acceptable salts of compounds, compositions that contain a "pharmaceutically acceptable carrier", and a claim drawn to a method of antagonizing the $\alpha_v\beta_3$ integrin, i.e., the following:

A method of antagonizing the integrin $\alpha_v\beta_3$ comprising administering to a patient in need thereof a compound according to claim 1 for a time and under conditions effective to antagonize the integrin $\alpha_v\beta_3$.

However, there does not exist a single disease, whether named in the specification or not, for which treatment is enabled. Certainly, enablement is lacking for treatment of circulatory disorders, thrombosis, cardiac infarction, coronary heart disease, arteriosclerosis, apoplexy, angina pectoris, cancer, osteoporosis, inflammation, infections, restenosis and rheumatoid arthritis. In addition, enablement is lacking for claims drawn to a "pharmaceutical composition", since this term implies an assertion of therapeutic efficacy. Applicants have argued in essence that an assertion of efficacy is tantamount to a demonstration of efficacy. However, applicants are not correct. It is not unusual for the hopes and expectations of a scientist (based on *in vitro* data) to be unfulfilled. Moreover, there is no evidence that any other investigator has been able to successfully treat ill patients using a $\alpha_v\beta_3$ antagonist. The assumption then is that all previous attempts at such treatment by medical researchers have met with failure. Perhaps applicants are aware of a reference which discloses that a given disease was in fact successfully treated using a $\alpha_v\beta_3$ antagonist. Were applicants to bring such a reference to light, the argument would then be that $\alpha_v\beta_3$ antagonism is a question of degree, and merely because one antagonist is sufficiently tenacious, does not mean that all other antagonists will be as effective. Consider, for example, Dechantsreiter (*J Med Chem.* **42**, 3033, 1999) and

Haubner (*J Am Chem Soc* **118**, 7881, 1996). In table I of Dechantsreiter and in table 2 of Haubner, data is presented on the propensity of peptides to inhibit the binding between the $\alpha_v\beta_3$ - integrin receptor, and a ligand. As is evident, minor changes in structure can lead to a reduction in efficacy of more than 1000-fold. There was also at least one example of elimination of activity in a compound containing RGD. The reality is that all areas of pharmacology are unpredictable. But specifically, the extent of binding of RGD peptides to cognate ligands is unpredictable. The adhesion can be very pronounced, or it can be very weak; either way, one cannot predict, *a priori*, which result will be obtained, merely by viewing a structure. And even if it were possible to do this, applicants have not explained how. In addition, applicants have not established the quantity of antagonism that is necessary to treat any of the named diseases; it remains entirely unknown at this time whether any of the claimed peptides will be effective in this regard. In addition, there is the matter of bioavailability and pharmacokinetics. Two compounds which are equally effective at antagonizing a receptor *in vitro* can exhibit very different efficacies *in vivo*. Given that receptor antagonism, bioavailability and pharmacokinetics are all "unpredictable", it follows that "undue experimentation" would be required to determine which of the claimed peptides will be effective to treat the named diseases [*Ex parte Forman* (230 USPQ 546, 1986)].

Notwithstanding the foregoing, if it is well known in the art that antagonists of $\alpha_v\beta_3$ are effective to inhibit angiogenesis *in vivo*, it is suggested that applicants submit the following

claim, accompanied by a reference which teaches the relationship in question:

A method of inhibiting angiogenesis comprising administering to a patient in need thereof a compound according to claim 1 for a time and under conditions effective to antagonize the integrin $\alpha_v\beta_3$.

Similarly, if it is well known in the art that antagonists of $\alpha_v\beta_3$ are effective to inhibit apoptosis, applicants can submit a claim drawn to inhibition of this (if there is support in the specification), accompanied by a reference which teaches this relationship. The same applies for a claim drawn to a method of inhibiting growth of bacteria.

✱

Claims 4 and 24-25 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

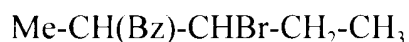
Claim 4 is drawn to a process of preparing a compound that is never isolated. However, the specification provides no guidance as to how one would proceed if the objective were to abstain from isolating the compound. If applicants believe that such instructions exist, applicants are requested to point out the page and line number.

A matter unrelated to the foregoing concerns claims 24-25. It is not apparent where support exists for the various derivatives. Applicants are requested to point out the location in the text.

✱

Claims 1, 2, 4-8, 11-31 are rejected under 35 U.S.C. §112 second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

- Claim 2 recites that the compound "is in the form of a single enantiomer or a single diastereomer". First, how is a compound that "is in the form of a single enantiomer" different from a single enantiomer itself? No difference is evident. Second, the term "diastereomer" is misused in this situation. The term at issue is a relative one; by way of analogy, one cannot have a "mirror image" of something that exists in and of itself, unrelated to anything else. Consider the following simple compound ("Bz" is benzyl, and "Me" is methyl):



This can exist as the R,R stereoisomer, the R,S stereoisomer, the S,S stereoisomer, and the R,R stereoisomer. Of these four stereoisomers, which one, in applicants opinion, represents the diastereomer? If there is adequate descriptive support for it, the following could be claimed:

A mixture comprising an optically pure compound according to claim 1, and a diastereomer thereof.

- The clarity of claim 4 would be enhanced by creating two separate claims, one for process (a), one for process (b), and one for process (c).
- Claim 4 is indefinite as to the process steps. Specifically, the claim fails to recite an isolation step for the final product. In response, applicants have argued that if a chemist undertakes a chemical reaction (i.e., $A + B \rightarrow C$), and if at the end of that reaction the product (i.e., "C") is present in a mixture which includes a solvent, and perhaps unspent reagents, the chemist is in possession of the product. The examiner is in disagreement with applicants on this point, and moreover, a proper analysis of this situation follows as much from logic and semantics as it does from the chemistry. If a person walks into a bank, is it the case that the person automatically acquires possession of the money that is present in the vault? As with the chemist, at least one additional step is necessary to achieve the objective.

- Claim 4 is indefinite as to the process steps. Specifically, the claim fails to recite that the reactions are carried out for a time and under conditions effective to achieve the intended result. Applicants have argued that a chemical process claim need not recite reaction conditions. The examiner does not require such. Applicants have also argued that if an applicant claims a chemical process, it is necessarily the case that all embodiments will "work", and that if any embodiments do not work, they are implicitly excluded from the scope of the claims. However, applicants have cited no Court case to this effect. If in fact a claim is drawn to a process that cannot "work", it is properly subject to rejections under §112, second paragraph (and perhaps §112, first paragraph). However, the analysis here is much less complicated than applicants are making it. Consider the following two claims:

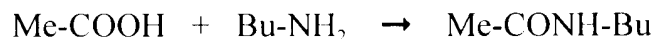
A process of converting "A" to "B" comprising the step of selecting a time period and conditions that would facilitate the recited conversion

A process of converting "A" to "B" comprising the step of selecting conditions that would make the recited conversion impossible

It appears to be largely a semantic matter. In one case, it is clear that the conversion will occur. In the other case, there is, at the very least, some uncertainty as to whether the selected conditions are consistent with the proposed conversion.

It is suggested that applicants amend the claim to recite that the "time and under conditions" are indeed effective to obtain a compound of formula I

- Claim 4 makes reference to a "cyclizing agent". However, there is no agent which inherently cyclizes anything. Consider the following simple reaction, i.e., the condensation of butylamine with acetic acid in the presence of a dehydrating agent (such as a carbodiimide):



Suppose instead that the two reactants (butylamine and acetic acid) were mixed together in the presence of a solvent and a so-called "cyclizing agent". In applicants opinion, exactly which cyclic structure would result? The answer, of course, is that there would be no cyclic structure. It is suggested that the claim recite the term "dehydrating agent". The same issue applies in the case of claim

22.

- In claim 4, the carbonyl oxygen atom, and the hydroxyl group are both missing from the first of the four "Z" substituents.
- In claim 4, step (b), the term "functional derivative" is used. The meaning of this is not clear. As a first step in the discussion, it would be helpful if applicants would provide an example of a "derivative" that is also not "functional".
- Claim 4 is indefinite as to what a "reactive derivative" means. The reality is that the compound of formula III is reactive to begin with. As a first step in the discussion, it would be helpful if applicants would provide an example of a "derivative" that is also not "reactive".
- Claim 4 recites that a "reactive derivative" of the compound of formula III is treated with a cyclizing agent. Suppose that one were to prepare an acid chloride (see p. 13, line 34, specification). The claim mandates that one would then take that acid chloride, and react it with the "cyclizing agent" to achieve the cyclic compound. It appears that the "cyclizing agent" is superfluous. In traversing, it would be helpful if applicants would provide an example of a "cyclizing agent" that they would propose to use in conjunction with an acid chloride.
- Claim 4, step (a) recites a cyclization step which results in the formation of the compound of claim 1. In proceeding to step (b), it appears that one can completely disregard step (a), i.e., bypass the cyclization step. This conclusion is reached because of the conjunction "or" at the end of step (a). Thus, how does one obtain the compound of claim 1 without a cyclization step? What is suggested here is to eliminate process (b) from claim 4, and to craft a separate claim which incorporates some of the discussion on page 14 (of the spec). This new claim should make clear what the starting material is.
- Claim 4 is drawn to a process of preparing a compound of formula I. Claim 4 is not drawn to a process of preparing a salt of a compound of formula I. However, part (c) mandates that a salt be formed, thus generating an inconsistency.
- Clarity of claim 4, process (c) would be enhanced by creating a separate claim which

recites the following:

A method of preparing a salt of a compound of formula I comprising

(a) treating a compound according to claim 1 with an acid or base to form a salt of the compound according to claim 1, and

(b) isolating the salt of step (a).

- Claim 5 is drawn to production of a pharmaceutical preparation wherein the dosage form is "suitable". What is the objective of the suitability?
- Claim 5 is drawn to a process for producing a pharmaceutical preparation; however, the claim does not mandate that the compound of claim 1, or any other specific component, is present in the composition at the end of the process. Thus, for example, one could mix the compound of claim 1 with a liquid carrier, remove the compound of claim 1, and subsequently add some other drug. Is this intended? Either of the following is suggested:

A process for preparing a composition that contains a compound according to claim 1 in combination with a solid, liquid, or semi-liquid excipient comprising mixing said compound with a solid, liquid, or semi-liquid excipient.

A method for preparing a composition that contains a compound according to claim 1 and a pharmaceutically acceptable carrier, said method comprising mixing a compound according to claim 1 with a pharmaceutically acceptable carrier.

- Claim 6 makes reference to "administration". What is the target of the administration? Is the target an animal, a plant, a petri dish, an apparatus, or something else?
- Claim 6 makes reference to "sustained administration". It is not clear what is meant by this. Some progress towards clarification could be achieved if applicants would provide an example of an excipient which would be entirely suitable and acceptable for "occasional" administration (e.g., a tablet), but would not, at the same time, be suitable for "sustained administration" (in the case of a tablet, if one were to take the tablet 10 times per day for 6 months, would that not be "sustained

administration"...?).

- Claim 6 makes reference to "at least one excipient". On what basis does one determine the number of excipients present? For example, if one has a mixture of ten different compounds, does this correspond to one excipient, or ten?
- In claim 7, the term "restenosis" is misspelled.
- Claim 7 is indefinite with regard to which "diseases of the circulation" and which "coronary heart diseases" are intended.
- Claim 7 is indefinite as to the process steps and endpoint. Applicants have provided evidence that the $\alpha_v\beta_3$ integrin can be antagonized. Applicants have argued that since this integrin can be antagonized, it follows therefrom that a variety of diseases can be successfully treated. Thus, in applicants view, antagonism of this integrin necessarily, and without exception accompanies any successful treatment (of a disease). It is suggested that the claim be amended to recite that the time and conditions of the administration are indeed effective to antagonize the integrin in question. Were it the case that treatment of osteoporosis is enabled (and it is not), the following would be suggested for the case of this particular disease:

A method for treating osteoporosis comprising administering to a patient in need thereof a compound according to claim 1 for a time and under conditions effective to antagonize the integrin $\alpha_v\beta_3$.

The same issue as indicated above applies in the case of claim 8.

- Claim 7 is drawn (in part) to a method of treating tumors. A tumor, however, is not a disease per se, but rather a manifestation of a disease. Accordingly, the question is, what is the intended effect of the treatment? Either of the following would be suggested, were the claim enabled:

A method for treating a patient afflicted with a tumor growth comprising administering to a patient in need thereof a compound according to claim 1 for a time and under conditions effective to antagonize the integrin $\alpha_v\beta_3$.

A method for inhibiting growth of tumor cells comprising administering to a patient in need thereof a compound according to claim 1 for a time and under conditions

effective to antagonize the integrin $\alpha_v\beta_3$.

- Claim 8 is indefinite with regard to the intended pathologies. One of the issues here is, how far "upstream" or "downstream" can one go in deciding whether the process is "supported or propagated" by angiogenesis.
- Claim 8 is indefinite as to the intended illnesses.
- In claims 1 and 20 are indefinite with regard to the derivatives that might be intended.
- Each of claims 1 and 20 recites the following:
"wherein optically active amino acids... can be in either their D or L forms"

This language suggests that there is a stereochemical form other than D and L. In the view of the examiner, there is no other form. In traversing, applicants are requested to provide an example of another a stereochemical form. In addition, the term "their" indicates possession. However, amino acids do not "own" any particular stereochemical form. The following is suggested:

wherein each optically active amino acid is of the D or L configuration.

- Claim 22 makes reference to a formula III, but does not provide a structure of such.
- In claim 23, the conjunction "or" should be present prior to the last Markush Group member.
- Claim 24 recites that "derivatized Gly is selected from **the** N-methyl, N-ethyl ... and C-methyl **derivatives**" What is meant by "the...derivatives"...? Does a C-alpha derivative of glycine include alanine?
- Claim 24 recites that "derivatized Gly is selected from **the** methyl, ethyl ... or benzyl esters of the side chain carboxyl group" However, glycine does not have a side chain carboxyl group.

- Claim 24, line 4 recites the following: "or benzyl esters". Here, the conjunction "or" should instead be *and*. The same applies in the case of claim 25.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). The practice of automatically extending the shortened statutory period an additional month upon filing of a timely first response to a final rejection has been discontinued by the Office. See 1021 TMOG 35.

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED AND ANY EXTENSION FEE PURSUANT TO 37 CFR 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

*

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Lukton whose telephone number is (703) 308-3213.

An inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.



✓ DAVID LUKTON
PATENT EXAMINER
GROUP 1800